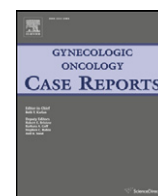


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Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case Report

Prolonged response to trabectedin in a heavily pretreated patient with metastatic endometrial carcinoma: A case report and literature review

Giulia Meoni ^{a,*}, Fabiana Letizia Cecere ^a, Imane Chaib ^b, Elisa Giommoni ^a, Francesco Di Costanzo ^a^a Medical Oncology 1, Azienda Ospedaliero Universitaria Careggi, Florence, Italy^b Laboratory of Molecular Biology, University Hospital Germans Trias i Pujol, Badalona, Spain

ARTICLE INFO

Article history:

Received 8 October 2011

Accepted 23 November 2011

Available online 3 December 2011

Keywords:

Endometrial carcinoma

Trabectedin

BRCA1

ERCC1

Chemotherapy

Introduction

Endometrial cancer is the most common gynecological malignancy and the third most common cancer affecting women in the western world. The majority of patients have disease confined to the uterus and have an excellent prognosis. However, a subgroup of patients has advanced primary disease or recurrence following primary treatment. The management of metastatic disease includes hormonal therapy (progestational agents, aromatase inhibitors, tamoxifen) and few cytotoxic agents (cisplatin or carboplatin, doxorubicin, ifosfamide and paclitaxel). The median overall survival (OS) of patients affected by metastatic endometrial carcinoma emerging from clinical trials is about 12 months. The response rate (RR) for first line of treatment ranges from 31% to 81% and for second line of treatment from 15% to 42% with relatively short duration.

Trabectedin (Yondelis®; ET-743) is an intravenous anti-neoplastic agent originally derived from the Caribbean marine tunicate *Ecteinascidia turbinata* and now produced synthetically. Trabectedin has shown variable levels of activity against several types of solid tumor including soft tissue sarcoma (STS), ovarian cancer, breast, melanoma, non-small cell lung cancer (NSCLC), prostate and endometrial cancer (McMeekin et al., 2009). Based on the results from a phase II randomized, non-blind, multicentre trial and several other non-comparative trials, the drug has currently been approved for the

treatment of advanced or metastatic STS progressed after conventional chemotherapy (at least one cycle of anthracycline- and ifosfamide-based chemotherapy) or ineligible for such treatment (Demetri et al., 2009). The drug is especially active in leiomyosarcoma and liposarcoma, the predominant histologic subtypes enrolled onto the registrative study.

In this paper we report the case of a prolonged response to trabectedin in a heavily pretreated woman with pulmonary metastases and pleural effusion from endometrial carcinoma.

Case report

On June 2002, a 60 year old woman (Caucasian) with no major comorbidities, underwent total hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic lymphadenectomy. The pathological analysis reported adeno-squamous endometrial carcinoma infiltrating two thirds inner of myometrium, pT1cN0M0, stage IC (TNM staging 5th edition). Subsequently the patient received adjuvant whole pelvic external beam radiotherapy (50 GY TFD) and then began follow-up without evidence of disease. The patient was referred to our institution on January 2005 when pulmonary disease recurrence was assessed by computer tomography (CT) and confirmed by positron emission tomography (PET). From January 2005 to September 2010 the patient received two sequential hormonal treatments (megestrol acetate and fulvestrant) and several lines of chemotherapy (carboplatin and Taxol, non-pegylated liposomal doxorubicin, thalidomide, metronomic cyclophosphamide and methotrexate, vinorelbine, mitoxantrone, 5-FU). Overall best response (OBR) for each treatment, related toxicity and sites of disease progression are detailed in Table 1. On September 2010 the patient developed performance status (ECOG PS) deterioration (PS: 1) with a symptomatic progression disease (cough, dyspnea, asthenia, hemoptysis). Blood chemistry analysis showed anemia (Hb 10 g/dl) and the echocardiogram revealed mild pericardial effusion. The CT scan demonstrated appearance of mild right pleural effusion and confirmed increase in the solid endobronchial lesion in the lower right lobar bronchus and in the number and size of pulmonary lesions, as shown in Fig. 1. Therefore, on 12th November 2010 the patient started the 10th line of treatment with trabectedin (1.2 mg/mq 24-hour intravenous continuous infusion every 3 weeks). At each single administration the patient received standard steroid premedication. Consistent with literature, the patient experienced elevated transaminases as major side effect, which ranged G3 (Common Terminology Criteria for Adverse Events version 4.0) after the third trabectedin administration

* Corresponding author at: Largo Brambilla 3, 50139 Florence, Italy. Fax: +39 55 7947538.

E-mail address: giulia.meoni@gmail.com (G. Meoni).

Table 1

Previous treatment: number of cycles, related toxicity, overall best response (OBR) and sites of disease progression.

Type of treatment	N° cycles	OBR	Related toxicity	Sites of disease progression	Reason for withdrawal
Megestrol acetate 160 mg PO daily	Daily for 15 months	SD	Vascular G2 (deep vein thrombosis)	Lung	PD
Fulvestrant IM 250 mg monthly	Monthly for 7 months	SD	Absent	Lung	PD
Carboplatin AUC 5 IV g1q21 + Taxol 175 mg/mq IV g1q21	4 (Carboplatin only from the 2nd cycle onward due to Taxol hypersensitivity)	PR	Neutropenia G3 Alopecia G2 pericardial effusion G1 Sinus tachycardia G2	Lung	PD
Myocet 75 mg/mq IV g1q21 + G-CSF	4	SD	Alopecia G2 Nausea G2	Lung	PD
Thalidomide 200 mg PO daily g1q42	1	NE	Peripheral neuropathy G3	NE	Neurotoxicity
Endoxan 50 mg PO daily + methotrexate 2.5 mg PO twice a day, 2 days weekly	Weekly for 1 month	PD	Absent	Lung	PD
Vinorelbine 60 mg/mq PO gg1,8q21	4	SD	Neutropenia G2 Anemia G1 Sinus tachycardia G2	None	Cardiotoxicity
Mitoxantrone 14 mg/mq IV g1q21	3	SD	Neutropenia G2	Lung	PD
5-FU 400 mg/mq IV bolus g1q14 + 5FU 2100 mg/mq over 48 h IV continuous infusion g1q14	4	SD	Absent	Lung and pleura	PD

NE: not evaluated; PD: progression disease; PR: partial response; SD: stable disease.

and resolved after a few days requiring intravenous hydration and steroid administration. Vomiting G1, diarrhea G1 and virus infection G2 were also present infrequently as side effects. After 2 cycles of chemotherapy, the patient achieved an evident clinical benefit consisting in the improvement of general condition (ECOG PS: 0) and the complete disappearance of cough, dyspnea and hemoptysis. The CT scan performed after the third cycle showed a dramatic partial response (PR), which was further improved by three more cycles of chemotherapy as shown in Fig. 2. No more toxicities were reported, so we established to administer chemotherapy up to 8 cycles. Due to this prolonged and impressive response to trabectedin we decided to assess mRNA expression levels of excision repair cross-complementing group 1 (ERCC1) and breast cancer 1 (BRCA1), which could be involved in trabectedin sensitivity as previously reported. Genetic tests were performed at the laboratory of molecular biology at University Hospital Germans Trias I Pujol in Badalona (Barcelona). Due to the bad quality of samples, they were able to amplify only ERCC1, with reported very low level (1.99). This result is not consistent with literature data which suggest that high ERCC1 expression levels are associated with major benefit from trabectedin. Trabectedin was stopped after the 8th cycle, when patient showed recurrence of respiratory symptoms and the CT scan revealed pulmonary disease progression (PD).

Discussion

The management of metastatic endometrial cancer is usually palliative and includes, as mentioned above, hormonal therapies and cytotoxic drugs which can be used both in single-agent and multi-agent regimens. Grade of differentiation, disease-free interval, location and extent of extra-pelvic metastases are well recognized prognostic factors.

Our patient received several lines of treatment and achieved a prolonged progression free survival (PFS) from first and second line hormonal agents whilst smaller benefit from chemotherapy, which was also associated with greater treatment related toxicity. For this reason we carefully assessed the eligibility of the patient before administering further chemotherapy with trabectedin.

As many other cytotoxic agents, the true mechanism of trabectedin cytotoxicity remains unclear. We know that the drug binds to the minor groove of DNA forming trabectedin-DNA adducts that bend DNA towards the major groove. In this way trabectedin interferes with the transcription-coupled nucleotide excision repair (TC-NER) pathway, blocks the G2/M phase cell cycle and inhibits activated gene transcription. The role of TC-NER is to recognize DNA lesions and to remove them from transcribed strands of expressed genes. ERCC1 is a component of this repair system. Trabectedin disrupts this repair

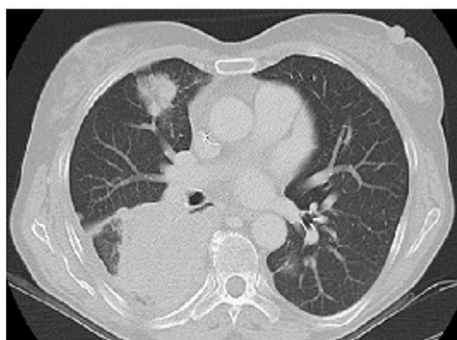


Fig. 1. CT scan at baseline: this figure shows the two major measurable lesions involving the inferior right lung lobe, the major causing stenosis of inferior lobar bronchus.

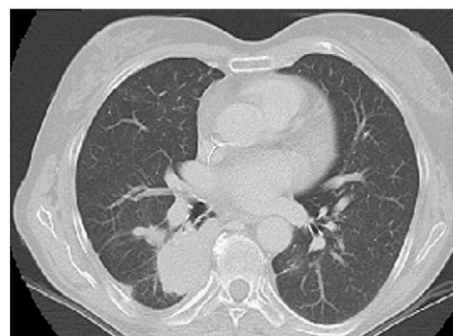


Fig. 2. CT scan after the 6th trabectedin cycle: this figure shows the complete disappearance of the anterior lesion and a major reduction in the posterior one, with improvement also of bronchus compression.

process preventing correction of DNA lesions by TC-NER and causing DNA damage through covalent bonds. Such lesions require homologous recombination repair (HRR) pathway proteins to repair the damage. Therefore solid tumor cells deficient in one or more HRR proteins, like BRCA1, are much more sensitive to trabectedin. Retrospective studies suggest that the ERCC1 and the BRCA1 status may represent a composite signature that could be used to predict clinical response to trabectedin in patients affected by STS (Italiano et al., 2011; Schöffski et al., 2011). In these patients high ERCC1 mRNA expression level is associated with improved although not statistically significant RR, median PFS and OS compared with low ERCC1 expression level. The same studies generate the hypothesis that BRCA1 genotype and low expression level correlate with major sensitivity to trabectedin. In this sense our data are not consistent with literature because in this case low ERCC1 mRNA expression level is associated with an impressive clinical response. This is possibly due to different reasons. Firstly, we are evaluating a different disease (endometrial carcinoma) from the one analyzed in the retrospective studies (STS) and so in our case trabectedin cytotoxicity could probably be induced by a different mechanism, even TC-NER independent. This is consistent with the observation that in our case trabectedin caused an impressive reduction in tumor burden, while this drug is usually associated with low RR and prolonged periods of stable disease in patient with STS. Secondly, we performed the quantification of the expression in the paraffin embedded sample of the primary tumor resected in 2002 and we do not know the genetic characteristics of metastases, which could show high ERCC1 expression levels instead. Assuming that ERCC1 expression levels are still low in the sites of metastatic disease, we observe that in this situation trabectedin shows similar behavior to other DNA damaging agents used in the treatment of different epithelial carcinoma, such as platinum compounds. In fact, as noted in patients affected by NSCLC, tumor cells with low ERCC1 enzyme level may be more sensitive to platinum-based regimens since they are less able to repair damaged DNA.

In conclusion this unconventional therapy for endometrial cancer confirms the urgent need to redefine and customize chemotherapy according to clinical characteristics as well as histochemical, molecular and genetic features.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

We gratefully acknowledge Doctor Rosell and Doctor Taron for their willingness to share with us this case and Doctor Chaib for his essential cooperation in conducting the genetic tests at the laboratory of molecular biology at the University Hospital Germans Trias i Pujol in Badalona (Barcelona).

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